PART XVI

*Guest Lecture* MECHANISMS OF PROGRESSION IN GLOMERULONEPHRITIS

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MECHANISMS OF PROGRESSION IN GLOMERULONEPHRITIS

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Since the beginnings of studies on nephritis, the question of why some individuals develop nephritis and others do not has occupied the attention of investigators. An equally important question is why some individuals with nephritis have a disease of short duration which heals clinically and histologically, whilst others have a prolonged course leading to renal failure. Clinical classifications are unable to help us: patients with acute nephritis, with a nephrotic syndrome, or found to have symptomless urinary abnormalities may equally heal or develop renal failure [1]. Histology is a little better in that it allows us to divide patients within these broad clinical classifications into different groups which have differing prognoses overall [1]. Some, such as mesangial proliferative and focal proliferative disorders rarely go on to renal failure, whilst other patterns such as membranous nephropathy go on to uraemia in about half those affected. Some, for example, focal segmental sclerosing lesions and mesangiocapillary patterns, are usually associated with eventual renal failure, whilst most patients with extensive crescent formation, whatever the glomerular pattern, show rapid entry into uraemia. Clinical behaviour allows us to predict to a limited extent; only a handful of patients have ever been described with minimal change disease and loss of proteinuria on corticosteroids, who have later developed renal failure [2–4]. Similarly, amongst those with focal segmental sclerosing lesions, those 20–25 per cent who respond to this treatment almost never become uraemic, whilst the majority of the others eventually do so.

However, within each of these histological or behavioural groups, some individuals heal and some become uraemic [1]. What is the difference between these patients, and what leads to persistence and progression of the disease? What, in the interplay of host and environmental balance, tips the balance against the patient? How can we give an individual prognosis — which is after all what both patient and doctor want, not descriptions of populations — and how could we manipulate the events to the patient’s benefit?

Unfortunately we still cannot answer any of these questions adequately, although some important clues have emerged in recent years which have led to a considerable shift in our concepts. Here, I will concentrate on mechanisms which might render potentially limited disease chronic, and particularly on what has been learned in the past five years or so.
Immunological mechanisms of progression

The tempting, simple hypothesis is to suggest that the continuation of the disease depends merely on the continuation of the initial insult. Rather surprisingly, there have been few studies of the effects of stopping regimes of immunisation or manipulation which lead to nephritis in animals. What data there are [6, 7] support the idea that, provided severe damage has not already occurred, resolution of the disease is found. At a clinical level one can test this hypothesis by examining the few cases in whom an identifiable immunogen is both present and can be eliminated [8–12] or disappears [13, 14]. In the majority of such cases, the disease regresses [8–12], although P. malariae infection is a notable exception [15]. However, we must ask how typical of glomerulonephritis as a whole is this tiny minority with identifiable persisting pathogens. By definition, there is a considerable antigen load, usually in the form of a severe continuing infection (e.g. on a heart valve or an infected juguloatrial shunt inserted for hydrocephalus) [12]. It is possible that these patients form a minority in whom host factors play an unimportant role, but a relatively normal immune system is overwhelmed by a very large antigen load. In contrast, one could postulate that the majority of cases with more insidious disease have an abnormal response to a relatively normal antigenic stimulus.

Further evidence in favour of this simple hypothesis comes from study of patterns of glomerular disease, and their relative incidence, in different parts of the world and in the recent past. A good deal of evidence points to a 20–50-fold decrease in the incidence of deaths from glomerulonephritis in the Western world over the past century, which is just flattening out, at about 70–100/106/annum [16]. This dramatic fall in the death rate from nephritis coincides with massive improvements in public health, with the elimination of many microbial and parasitic agents from the environment, and the recession in others such as streptococcal infections. In contrast, in the Third world where bacterial and parasitic infection is still rife, what evidence can be obtained indicated admission rates and death rates up to 100 times those found in the West and in China [15]. Thus, these data could be interpreted to indicate that persisting antigenic load is the major determinant of progression in glomerulonephritis in the majority of the world, and during most of history.

However, in the Western world we are, perhaps, dealing with a minority of patients in historic terms whose disease is predominately determined by host factors. This could of course operate through inefficiency in the elimination of antigens, with the persistence of nephritogenic stimuli, and this approach has found some favour [14], especially now that linkages of disease patterns and progression to the major histocompatibility complex have been described [18]. However, an alternative explanation is to suggest that persistence of disease depends upon the induction of secondary autologous immune mechanisms. This would have the advantage of explaining one of the greater paradoxes in the study of glomerulonephritis: that despite decades of search it has proved almost impossible to detect foreign antigens of microbial origin in the glomeruli of all but a tiny minority (perhaps a few dozen cases only) as discussed above. This has been explained as due to masking of the antigen by antibody and comp-
lement, or that antigen is present in very small amounts. However, if in the majority of patients with progressive glomerulonephritis secondary antibody-antigen systems are involved, then one would not expect that antigen would be present, other than in the early induction phase of the disease. In essence, these secondary autologous mechanisms would constitute a form of auto-immune disease.

One possibility is antibody against autologous antigens, as part of a failure to inhibit clones of cells producing antibody against normally ‘forbidden’ antigens. It is known that such antibody is induced as part of the T cell-independent polyclonal antibody response to many acute and chronic infections [19, 20] — witness the positive antinuclear factor tests together with other autoantibodies in many patients and animals suffering from chronic infections such as subacute endocarditis, malaria [21] or schistosomiasis. Izui et al [22, 23] have shown that endotoxin, known to induce polyclonal B cell activation, can induce anti-DNA antibody and DNA-anti-DNA complexes in mice. Mice infected with malaria develop anti-DNA antibody complexes [24, 25] and anti-DNA complexes are present in the kidney and blood [26, 27] in murine Schistosoma mansoni infection.

It is also possible that anti-idiotypic antibodies and other anti-antibodies produced as part of the normal process of antibody induction and control may react with antigens other than their ‘specific’ epitopes [28]. This important concept strikes at the usual ideas of the specificity of individual immunoglobulin molecules, since some ‘rheumatoid’ anti-IgG factors can also combine with nuclear antigens [29] whilst mouse myeloma protein and vitamin K apparently react with identical antibodies [30].

Do these observations have significance for human glomerulonephritis? Two possible autoantigens are already evident. The first is ssDNA or dsDNA, as just discussed. The ‘false’ positive antinuclear factor mentioned above usually depends on antibody directed against ssDNA or other nuclear antigens; antibody against dsDNA is usually not present in whole serum [31]. Two groups of workers, however, have found even antibody against dsDNA as well as DNA itself in large quantities — in cryoprecipitates or polyethylene glycol precipitates from serum of patients with idiopathic glomerulonephritis [31, 32]. Studies on eluates of human kidneys with idiopathic nephritis have yet to be performed. If this work is confirmed, it raises questions about the boundaries of autoimmune disease and the specificity of tests for SLE [33].

A second possible autoantigen is IgG itself. It is well known that in so-called ‘idiopathic’ cryoglobulinaemia (which itself usually complicates an identified or unidentified infection) IgM or IgG antoglobulin antibody is present in the circulation, together with IgM-IgG or IgG-IgG complexes, and that nephritis is common in this situation [34]. Antiglobulins (‘rheumatoid’ factors) are common in SLE and in some other forms of glomerulonephritis. McIntosh, Rodriguez-Iturbe, and their colleagues [35, 36] have pointed out that in post-streptococcal glomerulonephritis autologous IgG is often an antigen and participates in immune complexes deposited or forming in the kidney. They have suggested also that the IgG is rendered immunogenic by removal of some or all of its sialic acid (glycoprotein) moiety, probably by the neuraminidase present in streptococci as it is in many
other organisms. Here, perhaps, is one possible mechanism for exogenous alteration of autologous material, with the induction of autoimmunity to the altered molecule.

Non-immunological mechanism of progression

However, besides these secondary immunological mechanisms, much interest has been generated in the possibility that non-immunological mechanisms may operate in most forms of progressive renal disease [37], including those whose presumed initiation is through immunological injury. Already enough information is available to allow a tentative construction of vicious circles, which could lead to the perpetuation of damage without further intervention from either primary or secondary immunological mechanisms. Figure 1 shows an example of such a hypothetical system of loops, which even if it does not operate in vivo in the fashion depicted (which is likely given our present ignorance) at least allows us a framework to discuss these possibilities.

Glomerular damage is frequently followed by proteinuria, often massive. Does this have any harmful effect of itself? What is the most ‘pure’ form of clinical

Figure 1. Non-immunologic perpetuation of glomerular damage?
nephrotic syndrome we know, minimal change disease (lipoid nephrosis)? In the
majority of patients, repeated attacks of the nephrotic syndrome, or continued
proteinuria, do not lead to any fall-off in renal function [3]. However, renal
biopsy in a majority of such long-term patients with a minimal change nephrotic
syndrome reveals focal and segmental sclerosing lesions affecting part of some
glomeruli. These lesions — or lesions identical with them — can be found in other
patients who from the start run a course resistant to treatment with cortico-
steroids and who experience a steady decline in renal function, with more and
more extensive glomerulosclerosis [5]. What is the relation between these two
conditions? At the moment there is no agreement, but one school of thought
suggests that the segmental sclerosing lesions are the result of the continuing
proteinuria and that in a minority of patients this results in irreversible and pro-
gressive glomerular sclerosis [36]. Others believe that the two conditions are
morphologically similar but pathogenetically distinct. Until we understand more
of either condition, the argument cannot be resolved. However, can we support
the first proposition from experimental work in animals? Two sets of observa-
tions suggest that this view may be correct, and that proteinuria of itself can cause
irreversible glomerular damage. The first observation stems from the model of
repeated injections of the agent purine aminonucleoside in rats [39]. A single
injection leads to proteinuria, which can be maintained by repeated injections;
a glomerulosclerosis then appears in the glomeruli, which is proportional in
severity to the degree and chronicity of proteinuria. Second, if heterologous
proteins, e.g. BSA (but not ovalbumin) are injected in large quantities (5G/24h)
into rabbits for a few days, ‘overflow’ proteinuria is observed. However, even in
the acute stage during the injections it can be observed that some of the protein
in the urine is native rabbit albumin [40]. A few days after the injections of foreign
albumin cease, there is still profuse proteinuria, and by this time it is all native
rabbit albumin. At this point, examination of the glomeruli shows degeneration
and vacuolation of the podocytes of the glomeruli, with separation from the
basement membrane and disappearance of foot processes. These changes and the
degree of proteinuria are very dependent on the strain of rat used [41] so that a
 genetic element is important. Just the same podocyte changes are observed in
animals given purine aminonucleoside in single injection or repeatedly [39] in
experimental anti-GBM nephritis [42] and in human glomerulonephritis [43],
especially focal segmental glomerulosclerosis [44]. In renal allografts into
patients whose focal segmental glomerulosclerosis recurs in the allograft the
proteinuria may be immediate whereas the focal and segmental lesions may
become apparent in the glomeruli [45] only weeks or months later. Finally, if
increased delivery of albumin is through the basement membrane induced by
cationising the molecule, then a proportion of the proteinuria induced is auto-
logous, anionic albumin [46].

Other factors indicated in the figure could amplify this hypothetical ‘vicious
circle’. Recently, much work of great fascination and importance has been pub-
ished on ‘remnant’ kidneys and related topics from Brenner’s laboratory in
Boston [47–49]*. In rats in whom one and five-sixths nephrectomy has been per-
formed, profound changes in renal perfusion take place in the ‘remnant’ kidney
[47]. Although one and five-sixths of the kidney mass has been removed, so that

only 8 per cent of the kidneys remain, the glomerular filtration rate falls only to 29 per cent of normal and thus the single-nephron glomerular filtration rate rises to 275 per cent of normal in remaining nephrons [47]. Proteinuria quadruples [48], as does the excretion of anionic proteins, the excretion of neutral and cationic molecules, however, is unchanged. The podocytes show changes and the mesangium expands [49]. Thus, in the rat at least, the remnant kidney gives rise to proteinuria of itself; what is more Shimamura and Morrison [50] first pointed out that progressive glomerulosclerosis arises in such remnant kidneys. What haemodynamic events determine the appearance of this glomerulosclerosis, whether hyperperfusion or high pressure perfusion, and whether the effect is mediated through proteinuric damage to the podocyte or through changes in mesangial function is unknown. However, in human nephritis, it is well recognised that prolonged severe proteinuria is associated with a poor prognosis, whatever the underlying histopathology leading to the proteinuria [51]. Could it be that profuse proteinuria is a marker, not for more severe immunological assault on the kidney but for more severe haemodynamic alterations in remaining nephrons, or even that the proteinuria is itself the damaging event [38, 40]?

Observations are available on patients with only one kidney. This has generally been assumed to be a benign state, but more than twenty years ago it was reported [52] that a high proportion of such individuals died of renal failure, some with predominantly glomerular disease. More recently, detailed histological observations have been published on eight patients with renal agenesis, renal failure and focal segmental glomerulosclerosis [53], and it appears that the association is a strong one. The possibility that these cases are really unilateral renal dysplasia seems to have been excluded, but the effect does not seem to be present in children born with two kidneys, but nephrectomised in childhood [54]. In a very interesting case report Rivolta and colleagues [55] discuss an isografted human kidney in which partial nephrectomy was performed inadvertently by missing a polar artery; this isograft failed after ten years with focal and segmental lesions in the glomeruli.

Several reports have appeared since Kincaid-Smith [56] first drew attention to the focal and segmental sclerosing lesions which may be found in patients with reflux nephropathy and progressive deterioration in renal function [57–59]. At first, it was thought that the pathogenesis of these lesions might be immunological, perhaps as a result of auto-immunisation by renal tubular antigens released by the reflux-induced damage. Now, it appears more plausible that these lesions are another example of progressive scarring in ‘remnant’ kidneys. In agreement with this idea is the observation that proteinuria is nearly always profuse in these patients, often of dimensions similar to those seen in patients with a nephrotic syndrome. Hypertension may be present but is by no means invariable.

**Effects of diet on progression of renal failure**

Also intriguing are observations on the effect of diet in renal failure from glomerulonephritis or from other causes. An old observation [60] substantiated in many recent studies, shows that restriction of nitrogen (or phosphorus, or both) will increase survival in nephrotoxic nephritis, ameliorate the acute lesions of
five-sixths nephrectomy [49] in rats, will prolong life in the same model [61–62] and in anti-GBM nephritis [63, 64] again in the rat. Conversely protein overload shortens life. It is worrying that all these data come from a species in which, without any manipulation of the kidney, dietary restriction prolongs life [65] and spontaneous focal glomerulosclerosis occurs with ageing [66], which can be accelerated by protein feeding [67]. It is also difficult to know what the differential effect of nitrogen or phosphorus restriction was in these experiments: it is difficult to vary one without the other and even if the nitrogen intake is reduced and phosphorus intake carefully made equal [63] the phosphorus will not be in its usual dietary form.

Even so, there is evidence (admittedly uncontrolled) that dietary restriction will prolong life in renal failure in humans. The first observations suggesting this came from Kluthe et al [68] using a potato-egg diet, and others have made similar observations [69, 70], including after the use of ketoacid diets [71, 72]. How these effects in man and animals might be mediated is not at all clear but in dogs Shannon et al [73] showed, 50 years ago, that protein restriction could reduce glomerular filtration rate and renal blood flow. Solute restriction (without reference to the nature of the solute) may be the common factor in the various restricted diets, remembering that in most diets in most animals urea derived from protein will be the bulk solute unless the diet is specifically manipulated. In the case of alterations in phosphorus, however, other mechanisms may operate. Reduction in intake of phosphate in uraemic animals and man leads to a fall in PTH levels [74, 75], and another point with reference to the ketoacid diets is that the calcium intake tends to be higher. Thus it may be that some of these effects are mediated through reduction in parathyroid secretion. Not all the patients treated in the studies quoted above had glomerulonephritis, but the obvious implication is that non-immunological variables are important in the progression of renal failure from any cause.

The role of hypertension and vascular disease

What of the role of vascular disease and hypertension? It is well known that many normotensive patients with forms of glomerulonephritis which later prove progressive may show, even early in their disease, quite severe 'hyaline' lesions of the afferent arterioles which are disproportionate to not only the blood pressure but also the age of the subject [76]. These lesions are frequent, but infrequently commented on, and have been observed in early SLE, early membranous nephropathy, mesangiocapillary disease, and particularly focal glomerulosclerosis and IgA nephropathy at a time when blood pressure and renal function were normal. In our own study of the long-term evolution of membranous nephropathy [77] these lesions predicted a poor prognosis for renal function a decade later with some degree of precision whereas severity of glomerular changes did not. Their nature is quite unknown; in some cases vascular 'deposits' stain for C₃ complement and/or IgG; in most they are negative. However, in many cases where they are positive, they have been ignored as 'non-specific'. It may be so, but requires further study.

The intervention of hypertension in a patient with glomerulonephritis is
regarded as a bad sign by most nephrologists, although the evidence for this in man is slender. From studies of morbidity in patients with essential hypertension it would be very unlikely however to prove otherwise. What is more interesting is the possibility that hypertension might exacerbate the glomerulonephritis by a mechanism other than ischaemic glomerulosclerosis. Yet again, information on this topic has been available for some time but its relevance was not perceived. Knowlton in 1946 [78] superimposed deoxycorticosterone (DOC) on nephrotoxic serum nephritis, and noted worsening of the glomerular disease. Others [37,79–81] have repeated the same experiments, or used clip hypertension, or Heymann nephritis. In each case the outcome was the same; of the recent studies, proteinuria increased in all (although not in Knowlton’s original observations), the glomerular changes became worse, and the animals died sooner of uraemia. The experiments of Azar et al [82] are also relevant here, because they provide a possible link with the ‘hyperperfusion nephropathy’ just discussed. They studied kidney microperfusion and histology in rats submitted to unilateral nephrectomy and hypertension. There was an increase in single nephron glomerular filtration rate with elevated renal blood flow and increased transcapillary pressures. Further, Dworkin and colleagues [83] showed recently that protein-restricted diet will reduce single nephron glomerular filtration rate and proteinuria in proteinuric rats given a unilateral nephrectomy, then treated with DOC. This is further support for the idea that in this model, also, hyperperfusion or high pressure perfusion leads to direct renal damage.

Finally, there are some fascinating observations on the condition of familial dysautonomia, in which the kidney is intermittently subjected to high and low renal blood flow; these patients develop renal failure with sclerosing glomerular lesions [84, 85].

Conclusions

The mechanisms of progression in glomerulonephritis are most likely to be those which apply generally to all forms of progressive renal disease, and some of which are non-immunological at base. This may explain our failure to treat progressive glomerulonephritis by immune suppression or manipulation. By a combination of recent experiment and re-interpretation of older observations, a picture has emerged rapidly of hyper-perfusion (or high pressure perfusion) leading to progressive glomerulosclerosis, with an immediate prospect that renal failure might be delayed to a certain extent by reduction in dietary nitrogen, phosphorus, or total solute intake. The role of secondary autologous mechanisms, perhaps controlled via the major histocompatibility locus, seems to be of importance, at least in Western Europe where the majority of cases of glomerulonephritis do not arise from overwhelming infections and parasitaemias. However, a search for persistent immunisation is always worthwhile, since in the minority of patients in whom this mechanism can be demonstrated the disease may be controllable by removal of the antigenic stimulus, provided this can be achieved!
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